Imipenem Stability and Staining of Teeth

Scott E. Walker, Paula R. Walshaw and Helen Grad

ABSTRACT

The stability of imipenem in 5% dextrose in water (D5W) in the presence of cilastatin at 4°C and 23°C was tested over a 17-day period. In addition to visual inspection and pH, the concentration of imipenem was determined by a stability-indicating liquid chromatographic method. Within and between days analytical error, determined on replicate sample analysis, averaged less than 3%. The concentration of cilastatin was not measured. Thirteen human teeth were stored in sterile water, D5W, imipenem in D5W prepared fresh every 52-64 hours, or completely degraded imipenem diluted in D5W. The colour of each tooth was inspected during 36-days of storage at room temperature.

Imipenem solutions of 5 mg/mL in D5W lost more than 10% of their initial concentration when stored for more than 48 hours at 4°C or stored for more than six hours at room temperature. Protecting solutions from light had no significant effect on the degradation rate. The pH of all imipenem solutions declined during storage by approximately one pH unit and then began to rise. The colour of all solutions changed from being initially colourless to a very light yellow. Solutions stored at room temperature turned reddish brown within seven days.

There was no visible staining of intact tooth enamel or dentine by any solution during 36-days of storage at room temperature. Staining was restricted to root cementum, enamel pits and fissures containing organic debris and was greater with completely degraded imipenem solutions.

In conclusion, we recommend imipenem solutions should be stored at 4°C for no more than 24 hours prior to patient administration. We hypothesize that staining of teeth during imipenem therapy is the result of staining of accumulated plaque on the enamel surface. Imipenem does not appear to stain enamel or dentine directly.

Key words: imipenem, stability, teeth stains.

RÉSUMÉ

La stabilité de l'imipénem en présence de cilastatiné, dans un soluté de dextrose à 5 % (D5W) a été testée à des températures de 4 °C et de 23 °C sur une période de 17 jours. Outre les inspections visuelles et enlever à la vérification du pH, on a déterminé la concentration d'imipénem au moyen d'une épreuve de stabilité par chromatographie liquide. La marge d'erreur analytique pour une même journée ou entre deux journées, déterminée par une analyse d'échantillon répété, était inférieure à 3 % en moyenne. La concentration de cilastatine n'a pas été mesurée. On a déposé 13 dents humaines dans de l'eau stérile, du D5W, de l'imipénem dans du D5W fraîchement préparé toutes les 52 à 64 heures ou de l'imipénem complètement dégradé dilué dans du D5W. La couleur de chacune des dents a été inspectée au cours de la période d'entreposage de 36 jours à la température ambiante.

Les solutions d'imipénem de 5 mg/mL de D5W ont perdu plus de 10 % de leur concentration initiale enlever d'imipénem lorsqu'elles étaient entreposées pendant plus de 48 heures à une température de 4 °C ou pendant plus de six heures à la température ambiante. L'entreposage des solutions à l'abri de la lumière n'a pas eu d'effet notable sur le taux de dégradation. Le pH de toutes les solutions d'imipénem a diminué d'environ une unité de pH durant la période d'entreposage, pour ensuite augmenter. Toutes les solutions qui étaient à l'origine incolores sont passées au jaune très clair. Les solutions entreposées à la température ambiante sont devenues d'un brun rougeâtre après sept jours.

Aucune des solutions n'a provoqué de coloration de l'émail ou de la dentine des dents intactes au cours de 36 jours d'entreposage à la température ambiante. La coloration s'est limitée au cément, aux cuvettes et fissures de l'émail contenant des débris organiques et était plus prononcée avec les solutions d'imipénem complètement dégradé.

En conclusion, nous recommandons d'entreposer les solutions d'imipénem à une température de 4 °C et pour un maximum de 24 heures avant leur administration. Nous émettons l'hypothèse selon laquelle la coloration des dents au cours du traitement à l'imipénem serait le résultat de la coloration de de plaque accumulée sur l'émail. L'imipénem ne semble pas colorer l'émail ou la dentine de façon directe.

Mots clés : coloration des dents, imipénem, stabilité.

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INTRODUCTION

Adverse events related to the ingestion or use of drugs are common. Adverse events related to degradation products of a drug are less well recognized, but have been reported.[1,2] Neftel et al[1] reported that administration of penicillin-G, which was not freshly prepared, can increase the anti-penicillin antibody titres in patients. It has also been reported that administration of out-dated tetracycline products can cause proximal tubular necrosis and a Fanconi-like syndrome.[2]

Ku and O'Neill[3] reported that imipenem was observed to cause teeth stains in three patients receiving imipenem. Since all of these patients received imipenem under a Hospital-in-the-Home Program, and because a "visiting home nurse observed a brown, oily substance which discoloured the IV tubing,"[3] we hypothesized that the staining may have been related to the stability of the imipenem and degradation products of imipenem. This possibility was acknowledged by Ku and O'Neill, who also indicated that drugs were dispensed weekly to patients in this program.[3]

The stability of imipenem has been previously reported.[4,5] Zaccardelli et al[4] observed that imipenem lost more than 10% of the initial concentration after storage for one hour at room temperature in a total parenteral nutrition solution. Bigley et al[5] studied the stability of imipenem at 4°C and 23°C in a variety of intravenous solutions. In sodium chloride, imipenem was observed to retain more than 90% of the initial concentration for 72 hours at 4°C and for nine hours at 23°C, whereas, 5% dextrose in water (D5W) solutions of imipenem retained 90% of the initial concentration for only 24 hours at 4°C and for six hours at 23°C.

The intent of this study was to confirm the instability of imipenem in D5W solutions, and then evaluate the ability of imipenem solutions to stain human teeth *in vitro* over a 36-day period. The concentration of imipenem was evaluated by a validated stability-indicating liquid chromatographic method. The concentration of cilastatin was not evaluated in this study since it is reported to be more stable than imipenem.[4,5]

METHODS

Accelerated Degradation and Assay Validation

Following the development of the chromatographic system for imipenem, the suitability of this method for use as a stability-indicating assay was tested by accelerating the degradation of imipenem. A 4 mg/mL solution of imipenem (Primaxin®; imipenem and cilastatin sodium for injection - 500 mg, Lot # : S 1795; Merck Sharp & Dohme Canada, Kirkland, QC) in D5W was prepared. An aliquot of this solution (0.6 mL) was then mixed with 0.075 mL of 0.02 N HCl and placed in a polypropylene container (Diamed, Mississauga, ON). Samples were chromatographed at time zero and every 15 minutes for 240 minutes. Chromatograms were inspected for the appearance of additional peaks and the imipenem peak was compared between samples for changes in concentration, retention time and peak shape. Samples below a pH of 3 were also prepared but the imipenem degraded too quickly to be useful in critically evaluating the liquid chromatographic method of separation.

Following assay development, the imipenem content of Primaxin® (imipenem and cilastatin sodium for injection - 500 mg, Lot # : V 0263; Merck Sharp & Dohme Canada, Kirkland, QC) was determined using a primary reference standard of imipenem (imipenem susceptibility powder, 924 mcg/mg, Lot # : 7059A; Merck Sharp & Dohme, West Point, PA). Then the accuracy and reproducibility of standard curves was tested daily over three days and system suitability criteria (theoretical plates, tailing and retention time) were developed to ensure consistent chromatographic performance. On each day, an accurate weight of approximately 120 mg of Primaxin® powder (imipenem and cilastatin sodium for injection - 500 mg, Lot # : V 0263; Merck Sharp & Dohme Canada, Kirkland, QC) was dissolved in 10 mL of distilled water. After conversion based on the determined potency, the stock solution had a concentration of approximately 5.5 mg/mL. This stock solution was then further diluted with distilled water to obtain additional standards with final concentrations of approximately 5.0, 4.0, 3.4, 2.3, 1.7, and 0.6 mg/mL. When combined with a blank these standards served to construct a standard curve. Four microlitres of each sample were chromatographed in duplicate. As well, three quality control samples of imipenem were prepared (known concentrations of approximately 4.5, 2.8, and 1.1 mg/mL) and chromatographed in duplicate each day and their concentration determined and compared to the known concentration. Intra-day and inter-day error was assessed by the coefficient of variation of the peak area of both quality control samples and standards.

Chromatographic System

Imipenem was quantified using a reverse phase liquid chromatographic system with a mobile phase consisting of 1% methanol in distilled water. This mobile phase was pumped at 0.7 mL/min (Model 510; Waters

Scientific, Mississauga, ON) through a 15 cm x 4.6 mm, 3um column (Supelcosil ABZ+Plus; Supleco, Bellefonte, PA). Injections were made with an automated injector (WISP 712; Waters Scientific, Mississauga, ON). Imipenem was detected at 250 nm using a variable wavelength detector (Model 759A; Applied Biosystems Inc., Foster City, CA). Integration of the peak area at 250 nm was performed by a computer using chromatography acquisition and integration software (PC1000; Thermo Separation Products Inc., San Jose , CA). The imipenem peak area was subjected to least squares linear regression and the concentration, from the average of each sample, was interpolated from standard curves and recorded. Concentrations were recorded to the nearest 0.01mg/mL.

Stability Study

Sterile Primaxin® powder (imipenem and cilastatin sodium for injection - 500 mg, Lot # : V 0263; Merck Sharp & Dohme, Kirkland, QC) was reconstituted with D5W and diluted in a PVC bag containing D5W (nominal volume 100 mL; Lot ZP081471; Baxter Corporation, Toronto, ON) to prepare concentrations of approximately 5 mg/mL. Three aliquots of 10 mL of each concentration were stored in PVC containers at 4°C, at 23°C protected from light (using brown UV resistant bags) and at 23°C left exposed to light. Immediately following preparation and after 0.5, 1, 2, 3, 4, 7, 8, 9, 10, 14, 15, 16, and 17 days the imipenem concentration was determined by liquid chromatography. On each study day, fresh standards of imipenem were prepared as previously described and chromatographed to determine the imipenem concentrations. Tests of physical inspection and pH were also completed and the observations recorded.

Since the degradation of imipenem was observed to be rapid, to more accurately estimate the degradation rate at room temperature, a vial of sterile Primaxin® powder (imipenem and cilastatin sodium for injection - 500 mg, Lot # : V 0263; Merck Sharp & Dohme, Kirkland, QC) was reconstituted with D5W and diluted in a PVC bag containing D5W (nominal volume 100 mL, Lot #: ZP081471; Baxter Corporation; Toronto, ON) to prepare a concentration of approximately 5 mg/mL. Samples were chromatographed at time zero and every hour for at least 62 hours. This study was completed on two separate occasions.

Tooth Staining Study

After determining the stability of imipenem, 13 recently extracted human teeth were obtained through the Faculty of Dentistry at the University of Toronto. Selected teeth included ten erupted molars, one unerupted third molar and two central incisors. The crown and roots of each tooth were cleaned with a water-pumice slurry to remove bacterial plaque and salivary pellicle, such that prior to study all 13 teeth had a similar normal ivory colour. However, plaque or other organic debris in the pits and fissures of the molars were not removed. Of the 13 teeth, 10 erupted molars were arbitrarily selected for storage in (i) degraded imipenem solution diluted in D5W - two molars; (ii) imipenem in D5W solution prepared fresh every 52-64 hours - three molars; (iii) D5W - three molars, and (iv) distilled water - two molars. A central incisor was selected for storage in degraded imipenem and a second in imipenem that was freshly prepared every 52-64 hours. The single unerupted third molar was stored in degraded imipenem. Teeth were placed in each solution and stored at room temperature for 36 days. For teeth stored in fresh imipenem solutions, every 52-64 hours the teeth were removed from the degraded solution, rinsed in sterile water and placed in a freshly prepared imipenem solution. All teeth were removed from solution and inspected visually three times each week over the study period (0, 2, 4, 7, 9, 11, 14, 16, 18, 21, 24, 28, 30, 33, and 36 days). The observed colour of the teeth was recorded each day using the teeth stored in sterile water as a visual control for colour.

Data Reduction and Statistical Analysis

Means (± standard deviation) were calculated for replicated analyses. Reproducibility was assessed by coefficient of variation (CV). Mean results from different days of an identical test were compared statistically by least squares linear regression to determine if an association existed between the observed result and time. Log-linear and linear-linear fits for the data from the accelerated degradation study using acid were compared for goodness of fit by the Maximum Likelihood Method of Box and Cox.[6,7] Analysis of variance and the least significant difference multiple range were used to compare differences between storage conditions (temperature, protection from light). The five percent level was used as the *a priori* cut-off for significance.

In the stability portion of the study, imipenem concentrations were considered "within acceptable limits" if the concentration on any day of analysis was not less than 90% of the initial (day-zero) concentration. A solution was judged to be physically stable if there was no visual change in the colour or clarity of the mixture, the change in pH was less than 1.0 pH unit and no precipitate or other particulate formation was visually apparent.

RESULTS

Accelerated Degradation and Assay Validation

Imipenem degradation was observed to be pH dependant. An imipenem solution of 4 mg/mL in D5W, adjusted to a pH of 3.95 with HCl degraded in an apparent first order fashion (first order r^2 = 0.9963; compared to zero order r^2=0.6815) with a half-life of about 35 minutes. After 210 minutes, less than 1% of the initial imipenem concentration remained and there was chromatographic evidence of degradation products which were separated from and did not interfere with imipenem quantification (see Figure 1). The results of this investigation, that is, predictable degradation and chromatographic separation of degradation products and imipenem, indicated that this analytical method was stability-indicating.[8,9]

The standardization of Primaxin® powder using the reference standard indicated that Primaxin® was 48.64% imipenem by weight (estimates of 48.57% and 48.72%). Within day error observed with duplicate measurement of standards, during the three-day validation period and 14 study days, averaged 1.67% and was routinely less than 3%. Within day deviation from the expected concentration observed with standards, during the three-day validation period and 14 study days, averaged less than 1% and ranged from -1.12% with the 1.7 mg/mL standard to 3.61% with the lowest standard of 0.6 mg/mL. Similar performance was observed for the three quality control samples (4.5 mg/mL, 2.8 mg/mL and 1.1 mg/L) where replicate error averaged less than 1.70% and deviations from expected were generally within 5% and averaged between -2.2% and -1.4%, for all three samples. These analyses indicated that the imipenem concentrations were measured accurately and reproducibly and that differences of 10% or more could be confidently detected with acceptable error rates.[10] System suitability criteria were developed based on daily calculations of theoretical plates, tailing, retention time and accuracy observed during the validation period and were used to ensure continued chromatographic performance during the study period.

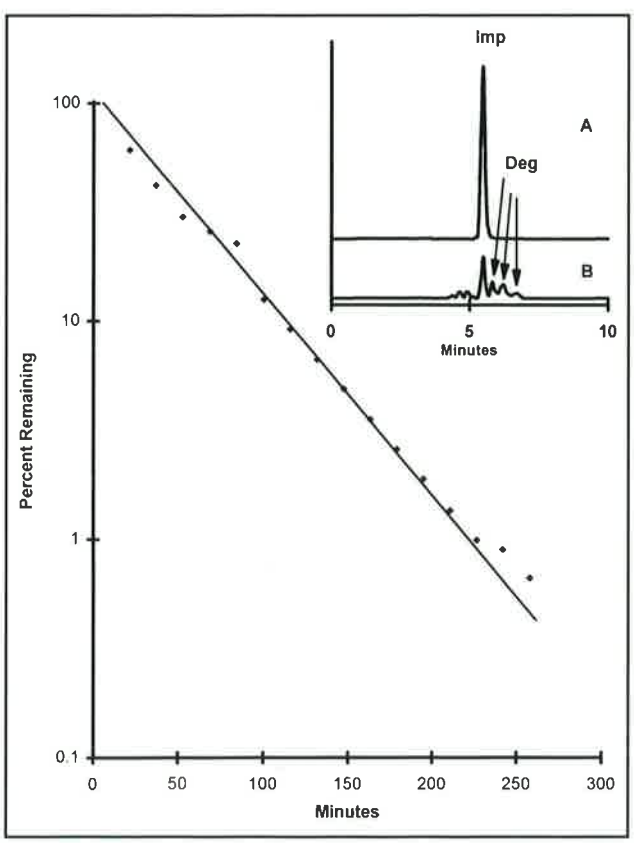

Figure 1. Rate of loss of imipenem during the accelerated study at room temperature in D5W adjusted to a pH of 3.95. As the imipenem concentration declined, degradation products could be observed in chromatograms. In the upper right corner; panel A shows the chromatogram observed at time zero with imipenem identified as 'Imp' and panel B shows the chromatogram observed at 60 minutes with 25.7% of the imipenem remaining and degradation products identified by 'Deg'.

Stability Study

At room temperature, solutions of imipenem in the presence of cilastatin degraded quickly. These solutions had initial concentrations of imipenem of approximately 5 mg/mL. After 12 hours, all solutions stored at 23°C contained less than 90% of the initial concentration (Table I). Degradation continued in a log-linear fashion with a half-life of approximately 1.68 days which was not significantly changed (p = 0.728) by protecting the solutions from light. Solutions degrading at this rate will reach 90% of their initial concentration within six hours. After nine days the solutions were dark brownish red and contained less than 5% of the initial concentration but were clear and remained free of particles. At this point chromatographic analysis of these solutions ceased. During this period of storage the pH changed, dropping from 7.42 on day zero to 6.29 on day two. Thereafter the pH steadily increased to 7.34 on day 17.

Solutions of imipenem stored at room temperature and chromatographed hourly also demonstrated a consistent decline in the imipenem concentration over a 62-hour period. The rate of loss averaged 1.42% per hour (range 1.33 to 1.63 % per hour), and a concentration of 90% of initial was achieved within 6.13 to 7.52 hours. In these studies, approximately 20-25% of the initial concentration remained after 62 hours.

Solutions of imipenem stored at 4°C also degraded. After 17 days storage approximately 60% of the initial concentration remained. While this indicates an average loss of about 3.5% per day, the initial rate of loss

was greater, such that after 48 hours only 90.3% of the initial concentration remained (Table I). After 17 days the solutions had progressed from a colourless solution when first prepared, through to a yellow colour on day seven to a yellow-orange colour on day 17. During this period of storage the pH declined from an initial value of 7.44 to 6.50 on day 9 and then began to increase achieving a pH of 6.72 on day 17.

Tooth Staining Study

The degraded imipenem solution was dark brownish red on day zero and was known to be completely degraded, containing no imipenem throughout the study period. The imipenem solutions that were prepared every 52 - 64 hours were estimated to degrade such that between 20 to 30% of the initial concentration remained at the end of the 52 - 64 hour storage period. After this period of storage these solutions were a yellow-orange or light reddish brown colour.

Over the 36-day storage period, the teeth stored in the completely degraded imipenem solution developed a dark brown staining on the roots, which would have originally been below the gum line. Intact enamel above the gum line was not discoloured by storage in any solution. However, the pits and fissures on the occlusal surface of the molars became stained a dark brown and some confined areas of some teeth developed a slight light brown (tan) discoloration where the enamel had been damaged. On completion of the study, the darkly stained roots of all four teeth stored in the completely degraded imipenem solution were scraped and the stain removed from one area of the tooth (Figure 2). Staining was confined to the cementum of the tooth as the underlying dentine was a normal ivory colour. This was confirmed by the total lack of stain on the cervical area of the roots of both incisors, where cementum had been abraded by tooth brushing in the mouth. Over the 36-day storage period the teeth stored in the imipenem solution which had been freshly prepared every 52-64 hours developed a light yellow staining of

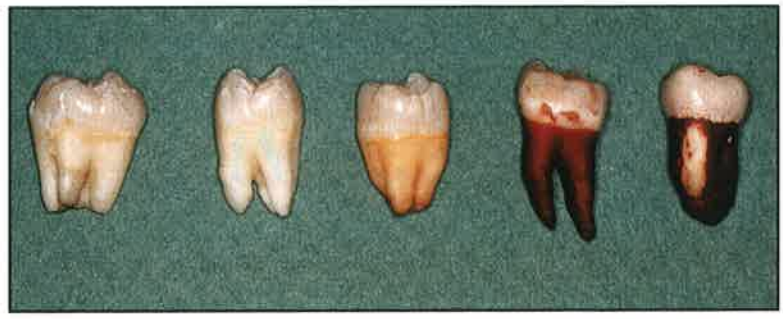

Figure 2. Five representative molars after 36-days storage in different solutions. The tooth on the far left was stored in sterile water for the duration of the study period. The tooth second from the left was stored in D5W. Neither tooth showed any change in colour over the study period. The middle tooth was stored in imipenem solution that was prepared fresh every 52 to 64 hours. This tooth developed a light yellow staining of the cementum (area below the gum line), but the enamel above the gum line had no visually apparent changes in colour and the pit and fissures on the occlusal surface (not shown) were also not stained. The two molars on the right were stored in the completely degraded imipenem solution for the duration of the study period and developed a dark brown staining of the cementum of the root of the tooth, which would have originally been below the gum line. The enamel above the gum line developed a slight light brown (tan) discoloration and some confined areas were stained a dark brown, including the pits and fissures on the occlusal surface of the molars. On completion of the study, the darkly stained root of one of the teeth (far right) was scraped and the stain removed from one area of one root. It would appear that the staining was confined to the root cementum as the underlying dentine was not stained dark brown.

Table I. Concentration of Imipenem in mg/mL*

Study Day	Storage conditions		
	4°C	Exposed to light 23°C	Light protected 23°C
0	5.26 (1.27)	5.06 (1.83)	5.27 (0.54)
0.5		4.30 (1.51)	4.27 (0.28)
1	5.06 (0.82)	3.70 (0.90)	3.90 (0.74)
2	4.75 (0.73)	2.80 (3.07)	2.73 (3.25)
3	4.52 (0.62)	2.17 (2.56)	2.09 (3.22)
4	4.35 (0.85)	1.15 (3.72)	1.10 (6.12)
7	4.05 (1.54)	0.35 (2.10)	0.31 (7.69)
8	3.97 (0.61)	0.22 (2.91)	0.17 (10.92)
9	3.88 (0.44)	ECBLOQ[b]	ECBLOQ
10	3.79 (0.40)	SNA[a]	SNA
14	3.40 (0.35)	SNA	SNA
15	3.33 (1.07)	SNA	SNA
16	3.25 (1.24)	SNA	SNA
17	3.17 (0.39)	SNA	SNA
Time to achieve 90%[c]	3.73 days	6.34 hours	5.97 hours
correlation coefficient (r)	0.9915	0.9909	0.9954

* numbers in parenthesis represent the coefficient of variation, expressed as a percentage, based on the concentrations found in three containers, chromatographed in duplicate.

[b] ECBLOQ indicates that the expected concentrations were well below the limit of quantification and so samples were not analysed. Lowest standard was approximately 0.5 mg/mL and values observed on days seven and eight were below this concentration.

[a] SNA indicates that samples were not analysed as concentrations were below the lowest standard.

[c] Time to achieve 90% of the initial concentration is based the on the first order degradation rate constant derived from log-linear regression of concentration- time data. The observed time to 90% is 48 hours for solutions stored at 4°C which is shorter than that predicted by regression.

the root cementum. The enamel crowns showed no visually apparent changes in colour (Figure 2), although the pits and fissures in the crown of the molars were very lightly stained (not shown in Figure 2). Teeth stored in the D5W or distilled water alone had no changes in colour over the 36-day study period to any portion of the tooth (Figure 2).

DISCUSSION

Bigley et al[5] studied the stability of imipenem at 4°C and observed that a 5 mg/mL solution of imipenem in D5W retained 91.8% of its intial concentration after 24 hours and 85.8% after 48 hours. At 23°C Bigley et al[5] observed that after six hours only 84.7% of the imipenem remained in a 5 mg/mL solution in D5W while 90.4% remained in a 2.5 mg/mL solution. Our results are very similar to those of Bigley et al[5] although we observed a slower rate of degradation. We observed that 5 mg/mL imipenem solutions stored at room temperature degrade rapidly achieving 90% of the initial concentration within six hours and solutions stored at 4°C in D5W retained more than 90% of the initial concentration for 48 hours, and by 72 hours only 85.9% remained. Therefore, both this study and Bigley et al[5] indicate that imipenem solutions stored at 4°C for more than 48 hours will have lost more than 10% of the initial concentration and would normally be considered as expired. Since solutions stored in the refrigerator are generally brought to room temperature prior to being infused, time spent at room temperature will further enhance the degree of degradation. Based on degradation rates observed in this study, we estimate that solutions stored for no more than 24 hours in the refrigerator and then allowed to stand at room temperature for an additional three hours, will retain more than 90% of their initial concentration. While changes in colour correlate closely with the degree of degradation for some cephalosporins,[11-13] changes in colour only become apparent after considerable degradation has occurred with imipenem. We observed that solutions containing between as little as 60-70% of the initial concentration are only light yellow or yellow in colour, and their physical appearance did not, therefore, indicate the degree of degradation.

In this study, we also observed that the cementum of teeth stored in completely degraded imipenem can become stained a dark brown, and that the cementum of teeth stored in imipenem solutions, which decreased in concentration from 100 to 20% of the initial concentration over a 52-64 hour period, were stained a very light tan colour. The main function of cementum is to attach fibres of the periodontal ligament to the tooth root and we hypothesise that the darkly coloured degradation products of imipenem were absorbed by the cells, fibres, and ground substance on the cementum surface. In contrast, the enamel was not stained, even after storage in completely degraded imipenem, except where organic debris was retained (as in the pits and fissures), or where the enamel had been damaged, possibly during the extraction process. This organic debris in the pits and fissures was stained much darker after storage in completely degraded imipenem solution.

Therefore, we do not believe that freshly prepared imipenem can stain intact enamel, and in fact have shown that even degraded imipenem cannot stain intact enamel. The staining of teeth, similar to that observed by Ku et al[3] most likely occurs if plaque is allowed to accumulate and the plaque itself becomes stained. Under clinical conditions, intra-oral staining of bacterial plaque might be more likely to occur in a debilitated patient or one who was unable to maintain effective oral hygiene. It is also possible that imipenem itself becomes bound to the plaque and then begins to degrade, turning brown. However, we observed the pits and fissures of teeth stored in solution prepared fresh every 52-64 hours to be more lightly stained than teeth stored in completely degraded drug, implying that the degradation product binds directly with cellular matter while fresh imipenem does not. Therefore, we hypothesise that staining, similar to that observed by Ku et al,[3] requires that degradation products be administered to the patient. This assumes that cilastatin is not involved in the staining of the teeth. This assumption is based on the relationship between the colour of the stain on the teeth stored in degraded imipenem solution, the colour of degraded imipenem (dark brown), and the colourless appearance of degraded cilastatin.[5] The only additional possibilities that might explain *in vivo* staining is that a metabolite of imipenem stains the teeth directly or that imipenem, in conjunction with other dietary compounds which stain teeth (coffee and tea), combine to produce a stain greater than either alone. Chlorhexidine stains teeth a dark brown[14-18] and enhanced staining has been reported to occur when chlorhexidine is administered with red wine, iron, coffee or tea.[14-17] Removal of chlorhexidine stains often requires abrasive dentifrices[18] or professional cleaning, as was reported by Ku et al[3] with the imipenem stains.

A recommended expiry date must consider that a prepared product may be stored for a period of time at both 4°C and room temperature. It is estimated that solutions stored for 24 hours at 4°C and then allowed to stand for no more than an additional three hours at room temperature would retain more than 90% of the initial concentration. Therefore, the use of imipenem in an outpatient program which results in dispensing fresh solutions only weekly will undoubtedly result in administration of solutions which would be regarded as

outdated. While this might reduce the effectiveness of the antibiotic, it may also expose patients to degradation products which could be toxic (like tetracyclines and Fanconi syndrome),[2] might increase the possibility of allergy (like penicillin and antibody titres),[1] or cause annoying disfigurement (staining of teeth).

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